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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,585	04/10/2007	Glen Ernst	101333-1P US	1463

22466 7590 10/16/2008

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GLOBAL INTELLECTUAL PROPERTY
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EXAMINER	
WILLIS, DOUGLAS M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
10/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,585	ERNST ET AL.	
	Examiner	Art Unit	
	DOUGLAS M. WILLIS	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *5-9 and 11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-20-06; 10-09-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

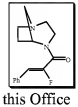
DETAILED ACTION

Status of the Claims / Priority

Claims 1-17 are pending in the current application. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/SE2004/001942, filed December 20, 2004, which claims priority under 35 U.S.C. § 119(e) to US Provisional Application No. 60/531,644, filed December 22, 2003.

Restrictions / Election of Species

Applicant's election of the following, with traverse, in the reply filed on September 15, 2008, is acknowledged: a) Group I - claims 1-4 and 10; and b) substituted diazabicyclo[3.2.1]oct-4-ylpropanone, diazabicyclo[3.2.1]oct-4-ylpropenone or diazabicyclo[3.2.1]oct-4-ylpropynone of formula I - p. 12, example 2, shown right below, and hereafter referred to as (*Z*)-1-(1,4-diazabicyclo[3.2.1]octan-4-yl)-2-fluoro-3-phenylprop-2-en-1-one, where D = -O-; E = -CR^1=CR^1-, wherein R^1 = -F and R^1 = -H; and G = -Ph. Affirmation of this election must be made by applicant in replying to this Office action.



Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. See MPEP § 818.03(a).

The elected species above has been found to be free of the prior art. Thus, the examiner has expanded the forthcoming prosecution to include all claims relevant to the genus of Group I, for a first Office action and prosecution on the merits.

Claims 5-9 and 11-17 were withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Thus, a first Office action on the merits of claims 1-4 and 10 is contained within.

Information Disclosure Statement

The information disclosure statement, filed October 9, 2008, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the foreign references (WO) are not provided. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-CR^1=CR^1-$; and R^1 = -H, -halogen or $-C_1$-C_4alkyl, does not reasonably provide enablement

for substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention(s) commensurate in scope with these claims. Substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and use substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, shown right;

I

(b) *Nature of the invention* - the nature of the invention is evaluation of substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I and the pharmacokinetic behavior of these substances in the human body as nicotinic acetylcholine receptor ligands;

(c) *State of the prior art - Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (**Jordan**, V. C. *Nature Reviews: Drug Discovery*, 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has extreme relevance to the synthesis of substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

> *Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.*
>
> *Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself*

the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).

(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and using substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl;

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E $\neq$ $-C(R^1)_2-C(R^1)_2-$; and R^1 = -H, -halogen or $-C_1.C_4$alkyl; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl. The specification lacks working examples of substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1.C_4$alkyl.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without

undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using substituted diazabicyclo[3.2.1]oct-4-ylpropanones or diazabicyclo[3.2.1]oct-4-ylpropenones and pharmaceutical compositions of the formula I, where E = $-C(R^1)_2-C(R^1)_2-$; and $R^1 \neq$ -H, -halogen or $-C_1$.C_4alkyl, is clearly justified.

Claims 1-4 and 10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I, does not reasonably provide enablement for *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention(s) commensurate in scope with these claims. *In vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and use *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I, shown right, as well as the myriad of *in vivo* hydrolysable precursors (*prodrugs*) of these substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones or pharmaceutical compositions, respectively;

(b) *Nature of the invention* - the nature of the invention is evaluation of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I and the pharmacokinetic behavior of these substances in the human body as nicotinic acetylcholine receptor ligands;

(c) *State of the prior art - Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Burger's with respect to the synthesis of *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I (Wolff, Manfred E., Ed. *Burger's Medicinal Chemistry and Drug Discovery - Fifth Edition,* New York: John Wiley & Sons, **1996**, vol. 1, pp. 975-976):

The design of prodrugs in a rational manner requires that the underlying causes which necessitate or stimulate the use of the prodrug approach be defined and clearly understood. It may then be possible to identify the means by which the difficulties can be overcome. The rational design of the prodrug can thus be divided into three basic steps: (1) identification of the drug delivery problem; (2) identification of the physiochemical properties required for optimal delivery; and (3) selection of a prodrug derivative that has the proper physiochemical properties and that will be cleaved in the desired biological compartment.

The difficulty of extrapolating data from animal to humans encountered during toxicokinetic and toxicologic studies with drugs is amplified with prodrugs, since not only metabolism of the active moiety might differ, but also its availability from the prodrug. As a matter of fact, there is presently no published rational for the conduct

of animal and human pharmacokinetic programs during prodrug research and development.

(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and using *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diaza-bicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I;

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I. The specification lacks working examples of *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir.

1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using *in vivo* hydrolysable precursors (*prodrugs*) of substituted diazabicyclo[3.2.1]oct-4-ylpropanones, diazabicyclo[3.2.1]oct-4-ylpropenones or diazabicyclo[3.2.1]oct-4-ylpropynones and pharmaceutical compositions of the formula I, is clearly justified.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

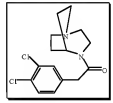
Claims 1, 2 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bowen, et al. in US 5,679,673, in view of Patani, et al. in *Chem. Rev.*, 96, **1996**, pp. 3147-3176.

The instant application recites substituted diazabicyclo[3.2.1]oct-4-ylpropanones and

I

pharmaceutical compositions of the formula I, shown to the left, where D = -O-; E = $-C(R^1)_2-C(R^1)_2-$, wherein R^1 = -H; and G = -Ph, substituted with two $-CH_3$ (C_1-C_6alkyl) groups, as nicotinic acetylcholine receptor ligands, useful in the treatment of disorders such as Alzheimer's disease, anxiety, depression, smoking cessation and Tourette's syndrome.

Bowen, et al. (US 5,679,673), as provided on the IDS, teaches substituted diazabicyclo[3.2.2]nonan-4-ylethanones and pharmaceutical compositions of the formula I, shown to the right, where D = -O-; E = $-C(R^1)_2-$, wherein R^1 = -H; and G = -Ph, substituted with two -Cl atoms, as derivatives for central



nervous system (CNS) disorders and useful in the treatment of neurodegenerative diseases [p. 9, column 14, line 65, example 4; pharmaceutical compositions - p. 10, column 16, lines 17-65].

Patani, et al. (*Chem. Rev.*, 96, **1996**) teaches -Cl atoms and $-CH_3$ groups as bioisosteric and isolipophilic, which exert similar biological activity [p. 3154; column 1, ¶ 1; section A4].

The differences between the applicant's instantly recited diazabicyclo[3.2.1]oct-4-ylpropanones and pharmaceutical compositions of the formula I and Bowen's substituted diazabicyclo[3.2.2]nonan-4-ylethanones and pharmaceutical compositions of the formula I are:

a) the instantly recited diazabicyclo[3.2.1]oct-4-ylpropanones and pharmaceutical compositions of the formula I and Bowen's substituted diazabicyclo[3.2.2]nonan-4-ylethanones and pharmaceutical compositions of the formula I are homologs; and b) G = -Ph, substituted with two $-CH_3$ (C_1-C_6alkyl) groups, in the instantly recited diazabicyclo[3.2.1]oct-4-ylpropanones and pharmaceutical compositions of the formula I, whereas G = -Ph, substituted with two -Cl atoms in Bowen's substituted diazabicyclo[3.2.2]nonan-4-ylethanones and pharmaceutical compositions of the formula I.

The MPEP § 2144.09 states "Compounds which are homologs, differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. {*In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977)}.

Similarly, the courts have recognized that *even in the case of homologs, a rejection on the basis of structural relation may be improper, with the critical question to be answered being whether the moieties of the molecules under consideration are considered 'homologous' under some available definition or whether they 'are sufficiently similar from the standpoint of structural similarity, so that those now claimed would be suggested to chemists from those disclosed and would be expected to have like properties.* (See *Ex parte Burtner and Brown,* 121 USPA 345 (1951).

Moreover, the courts have recognized that *when expectation of similar properties stands unrebutted, it necessarily follows that expectation of similar uses also stands unrebutted, [with] expectation of similar use necessarily implying expectation of substantially equivalent substitute(s). Furthermore, there is no logical basis for distinguishing patentably between a*

prior art [homologous] compound and a claimed novel compound prima facie obvious therefrom, even where a previously unknown or unobvious use has been found, where that use nevertheless inheres in both compounds and it is the compound per se that is claimed. {See In re Hoch, 57 CCPA 1292, 428 F.2d 1341, 166 USPQ 406 (1970)}.

Consequently, since: a) Bowen teaches substituted diazabicyclo[3.2.2]nonan-4-ylethanones and pharmaceutical compositions of the formula I, which are homologous with the instantly recited diazabicyclo[3.2.1]oct-4-ylpropanones and pharmaceutical compositions of the formula I and have G = -Ph, substituted with two -Cl atoms; b) Patani teaches -Cl atoms and -CH_3 groups as bioisosteric and isolipophilic, which exert similar biological activity; c) the MPEP § 2144.09 states that compounds which are homologs are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties; and d) the courts have recognized that an unrebutted expectation of similar use may imply expectation of substantially equivalent substitutes (i.e. homologous compounds), one having ordinary skill in the art, at the time this invention was made, would have been motivated to combine the teachings of Bowen and Patani and: a) form homologs of Bowen's substituted diazabicyclo[3.2.2]nonan-4-ylethanones and pharmaceutical compositions of the formula I, where G = -Ph, substituted with two -CH_3 (C_1-C_6alkyl) groups, with a reasonable expectation of success and similar therapeutic activity, rendering claims 1, 2 and 10 obvious.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/
Examiner, Art Unit 1624

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Supervisory Patent Examiner, Art Unit 1624